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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM Date: November 1, 2000

SUBJECT: **Atrazine**: Cancer Peer Review Committee Meetings - Provisional Conclusions

FROM: Roger Hawks, Ph.D.
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THROUGH: Bill Burnam, Chairman, Cancer Assessment Review Committee
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and

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This memorandum contains the provisional conclusions from the Health Effects Division (HED) Cancer Peer Review Committee (CARC) meetings held subsequent to the Fifth CARC meeting held in August of 1996 (Memorandum, From Melba Morrow, D.V.M.; to Joycelyn Stewart, Ph.D., July 23, 1996). New data submitted by the Registrant quickly rendered deliberations from this meeting inadequate for through evaluation of the carcinogenic potential of atrazine. Thus, a final written report from this meeting was never prepared. The CARC meetings held subsequent to the Fifth CARC meeting were held October 13, 1999, April 12, 2000 and October 19, 2000. The conclusions from these three meetings are considered to be provisional pending receipt and review of the written comments from the June 27th to 29th , 2000 FIFRA Science Advisory Panel (SAP) meeting which convened to consider a hazard assessment for atrazine presented by HED.

A more detailed discussion and presentation of the data used in evaluating the carcinogenic potential of atrazine at these three CARC meetings will be contained in a document which will be released upon incorporation of comments from the SAP. This document will update, replace, and finalize a preliminary, draft document entitled "Carcinogenicity Hazard Assessment and Characterization" which was presented to the SAP on June 27th to 29th, 2000.

CARC members present:

Lori Brunsman _____

Joycelyn Stewart _____

Clark Swentzel _____

Mike Ioannou _____

Victoria Dellarco _____

Karl Baetcke _____

Virginia Dobozy _____

Marion Copley _____

Bill Burnam _____

Jess Rowland _____

Nancy McCarroll _____

Linda Taylor _____

Richard Hill (OSPC)

Others present:
Pam Noyes (SRRD - nonvoting)
Cathy Eiden (HED - nonvoting)

John Pletcher (pathology consultant - nonvoting)
Roger Hawks (HED - voting)

The afore-mentioned three most recent HED CARC meetings discussed data pertaining to several questions relating to the carcinogenic potential of atrazine. These questions were:

1. Is atrazine treatment associated with an increased incidence and/or early onset of mammary gland and pituitary tumors in females of the SD rat strain, but not in male SD rats or CD-1 mice and F-344 rats of either sex?

2. Has the mode of action (MOA) for cancer in the rat, proposed by the Registrant, been supported by the data available? Concurrent with this, have mutagenicity and direct estrogenic potential of atrazine been found to play a significant role in the carcinogenic action of atrazine in the rat?

3. Are the available epidemiology data sufficient to support an association between atrazine exposure and mammary cancer, or any other type of cancer, in humans?

4. Does the proposed MOA for cancer in the rat have relevance to humans?

5. What is the cancer classification for atrazine?

In response to the first question, HED CARC determined that there was sufficient evidence to conclude that atrazine is associated with mammary and pituitary tumors in female SD rats, but not in male SD rats or CD-1 mice and F-344 rats of either sex.

In response to the second question, HED CARC concluded that the data available supported the proposed MOA associated with the carcinogenesis seen in female SD rats following atrazine exposure. The MOA referred to here is a cascade of events resulting from an attenuation of the proestrus afternoon luteinizing hormone (LH) surge which results in increased number of days in estrus associated with prolonged/increased exposure of endocrine-responsive tissues to estrogen and prolactin. In addition, mutagenicity and direct estrogenic activity were concluded to not play a significant role in the carcinogenic effects of atrazine.

In response to question three, the HED CARC concluded that the human epidemiology database did not provide sufficient evidence to associate atrazine with human cancer of any tissue.

For question four, the HED CARC concluded, in regards to the relevance of the MOA to humans, that the MOA established for rat carcinogenicity was not relevant to humans. CARC concluded that, though hypothalamic disruption of pituitary function (*i.e.* - attenuation of the LH surge) and resulting estrous cycle disruption may be occurring in humans following atrazine exposure, the hormonal environment resulting from these events would be expected to be much different from the

environment seen in the rat. The prolonged/increased exposure to estrogens and prolactin seen the rat would not be expected to be occurring in the human as level of these hormones are low in humans with attenuated proestrus afternoon LH surges.

In response to the fifth question, HED CARC (in a unanimous vote), in accordance with the 1999 review draft of the Guidelines for Carcinogen Risk Assessment, classified atrazine as "Not Likely to be Carcinogenic to Humans".

The basis for classification rested primarily on the following factors:

- The tumors associated with atrazine exposure are seen in only one sex and strains of rats;
- An MOA has been established for these tumors and this MOA is not relevant to humans. Previously CARC had found atrazine to be a "Likely" carcinogen and the draft document presented to SAP in June reflected this opinion. This classification assumed that a pair of human models of anovulatory conditions (polycystic ovarian syndrome and hypothalamic amenorrhea) were valid models of the above-described rat MOA in humans. The deliberations at the June SAP meeting clearly reflected to SAP's view that these models were not valid models to be used in evaluating the relevance of this MOA to humans. These SAP comments were considered at the most recent, October 19, 2000 meeting of CARC and played a major role in the decision to change the classification from "Likely" to "Not Likely";

- Mutagenicity and direct estrogenic activity do not play a significant role in atrazine-associated carcinogenicity.

This classification is considered provisional. The classification will be reconsidered and made final following receipt and review of a written SAP report from the June, 2000 SAP meeting on atrazine.

Also discussed at the October 19, 2000 CARC meeting were some topics introduced by the SAP at their June, 2000 meeting. These were:

- a concern that decreased body weight in high dose groups in a chronic bioassay using the F-344 rat may have lowered mammary tumor incidence in these groups;

- a possible appetite suppressant effect of atrazine;

- a concern that bioassay data be scrutinized more closely for signs of increases in ovarian tumors and NHL;

- a possible effect of atrazine on aromatase (CYP19) activity.

A more detailed discussion and presentation of the data used by CARC in evaluating the carcinogenic potential of atrazine is contained in a document which will be released upon incorporation of SAP comments. This document will update, replace and finalize a preliminary, draft document entitled "Carcinogenicity Hazard Assessment and Characterization" which was presented to the SAP at its June 27th to 29th, 2000 meeting.